SUMMARY OF STATEMENT

The Biotechnology Industry Organization and the Pharmaceutical Research and Manufacturers of America support the following:

FIVE-YEAR RENEWAL OF PDUFA

PDUFA expires on September 30, 1997, and must be renewed without delay. The program has been a success. Industry agreed to pay $327 million in user fees during 1993-1997, enabling FDA to hire 600 new reviewers and cut review times from 29.2 months in 1992 to 15.5 months in 1996. Thus, safe and effective new medicines are reaching patients 14 months earlier. FDA and industry have developed a legislative framework for Congress to consider that would renew PDUFA for five more years and not only continue to reduce FDA review times but for the first time address the drug-development phase, in exchange for which industry would pay at least 21 percent more in user fees. This would allow the agency to continue PDUFA without interruption and implement new performance goals, enabling patients to receive new medicines 10 to 16 months sooner.

LEVEL FUNDING FOR FDA

While FDA funding is not directly at issue in this hearing, the subject is necessarily involved. Without funding for FDA in FY98 at least equal to that in FY97, the user-fee law – and all the progress that has been made under the law to benefit patients – will be negated. As Members of this Committee have noted, without level funding the fees would just be used for general deficit reduction – not to benefit patients. The Administration has in effect proposed an 8 percent cut for FDA in FY98 and a 13 percent cut in the budget for human-drug approvals. Without level funding for FDA, there would be a substantial slowdown in drug development and review times, to the ultimate detriment of patients. With industry spending $19 billion on R&D to develop new cures this year and U.S. taxpayers providing $13 billion to NIH for biomedical research, it makes no sense to cut FDA's budget by $68 million and delay approval of these new cures.

FDA IMPROVEMENT LEGISLATION

Industry's FDA-improvement proposals reflect consensus views that emerged during the 104th Congress and would complement the PDUFA framework by structurally changing critical agency practices and procedures. The aim of the provisions in the PDUFA framework and the FDA-improvement proposals is the same: to make new medicines available to patients sooner.

STATEMENT

Mr. Chairman and Members of the Subcommittee, I am Gordon M. Binder, Chairman and Chief Executive Officer of Amgen, a California-based biotechnology company. It is a pleasure for me to appear before the Subcommittee today.

I am submitting this statement on behalf of the Biotechnology Industry Organization (BIO) and the Pharmaceutical Research and Manufacturers of America (PhRMA). These organizations represent the country's major research-based pharmaceutical and biotechnology companies. I appreciate the opportunity to discuss the reauthorization of the Prescription Drug User Fee Act of 1992 (PDUFA) and enactment of other FDA-improvement legislation.

To attempt to put today's hearing in perspective, Mr. Chairman, I would like to note that never has there been a time when the promise of biomedical research has been greater. Scientists are exploring the secrets of genes – the basic units of life. This research is revealing the sources and biochemical pathways of disease. Increasingly, new medicines will be used to prevent disease -- rather than just treat disease. What we are really talking about in this hearing, then, is ensuring that FDA will be able to facilitate – not frustrate – the gathering biomedical revolution that will, as

one Harvard professor noted, "produce pharmaceuticals of the kind that we don't even foresee now."

That's why reauthorization of the 1992 user-fee program is so crucial – it would enable the agency to maximize the benefits of the incredible advances that are being made in biomedical research. Few Government initiatives have been so successful for so many people in such a short period of time. PDUFA has been a success for Congress, FDA, and industry. It has also been a success for the people who matter the most – millions of patients throughout the world whose lives have been improved because they are receiving new medicines more quickly than ever before.

PDUFA, which represented an historic agreement between Congress, the FDA, and industry, is based on four bedrock principles: It (1) represents a long-term commitment by Congress, (2) requires that the fees be additive to FDA's baseline appropriations, (3) dedicates the fees to the drug-review process, and (4) provides quantifiable performance standards. Under the 1992 law, industry agreed to pay $327 million in user fees during 1993-1997, which enabled FDA to make improvements in the drug-review process and hire 600 additional reviewers.

PDUFA has produced dramatic results. In 1992, the mean approval time for a New Drug Application (NDA) was 29.2 months. In 1996, for drugs for which user fees were paid, the mean approval time for an NDA was cut nearly in half to 15.5 months. In 1992, FDA approved 26 New Molecular Entities (NMEs). In 1996, the agency approved more than twice that figure – 53 NMEs – plus 9 new biologics compared with 6 in 1992.

Among the new medicines approved in 1996 were two new protease inhibitors and a non-nucleotide transcriptase inhibitor to fight HIV and AIDS, as well as a drug to combat a leading cause of blindness in AIDS patients; four new drugs for orphan diseases; five new anti-cancer drugs; the second new drug for Alzheimer's Disease; two new mental-health medicines – an anti-depressant and an anti-psychotic; an important new cholesterol-lowering drug; two new medicines in a new class of asthma drugs; two new treatments for multiple sclerosis; two new drugs for glaucoma, and the first new insulin product in 14 years.

We do not plan to stop there. Pharmaceutical and biotechnology companies are investing almost $19 billion, 21 percent of sales, to discover and develop many more live-saving, cost-effective medicines. Hundreds of medicines and vaccines are already in the pipeline, including 96 in development for heart disease and stroke, 215 for cancer, 122 for AIDS, 125

for infectious diseases, 64 for mental illness, 132 for other medical problems of older Americans, and 284 biotechnology products.

FIVE-YEAR RENEWAL OF PDUFA

As effective as PDUFA has been, much remains to be done. The 1992 law focused on the drug-review process. It did not affect the clinical-development phase of the regulatory process.

The drug discovery and development process – which can take up to 15 years at an average cost of about $500 million for a new drug in 1990 dollars – is divided into three distinct phases. The first phase, early research and preclinical testing of new compounds, cannot benefit much from FDA improvements. During the clinical-development phase, new compounds are tested in humans for safety and efficacy in large, complex trials. Finally, in the third phase, the drug-review process, FDA reviews a drug-sponsor's NDA.

The 1992 law provided a basis for expediting the final, drug-review phase of the regulatory process. This was the shortest of the three phases. The 1992 law did not address the other two phases of the regulatory process.

Thanks especially to the leadership of David W. Blois, Ph.D., Vice President Worldwide Regulatory Affairs at Merck Research Labs, and Dr. Michael Friedman, lead Deputy Commissioner of Food and Drugs, industry and FDA have developed a legislative framework for Congress to consider that would renew and improve the user-fee law for five more years. In exchange for the payment by industry of at least 21 percent more in user fees, FDA would streamline the clinical-development phase as well as the drug-review phase. The proposed framework contains many industry proposals to expedite clinical development, including specifications regarding timelines and performance goals.

Industry regulatory experts estimate that the provisions in this legislative framework would reduce drug development and review time by 10 to 16 months.

Under the proposed legislative framework, FDA would undertake many comprehensive improvements and establish quantifiable, measurable timelines and performance goals. FDA also would be able to acquire and install a paperless, electronic information system to process all required submissions and applications, which should be of major help in improving efficiency and productivity.

A five-year extension of PDUFA is required so that FDA will be able to install the new information system and continue operations without interruption, plan ahead, allocate resources, and implement its agreed-upon timelines and performance goals in an incremental way, just as it has under the 1992 law. On the other hand, a one-year extension would raise doubt about Congress' long-term commitment to PDUFA, make it difficult, if not impossible, to start a long-term computer-system development project, undermine the careful, incremental way in which FDA has planned to implement changes, and require the agency to waste valuable staff time again next year in addressing reauthorization of the user-fee law.

The PDUFA legislative framework, including general provisions and specific performance goals, is discussed in Attachment A to this statement.

LEVEL FUNDING FOR FDA

While FDA funding is not directly at issue in this hearing, the subject is necessarily involved. Without level funding for FDA, the user-fee law – and all the progress that has been made under the law to benefit patients – will be negated.

Accordingly, industry believes it is essential that FDA be funded in Fiscal Year 1998 at the level of appropriations enacted for the current fiscal year, adjusted for inflation, and designating similar level funding for the human drug development and review process. In particular, industry strongly supports keeping budget authority for FDA salaries and expenses at $820 million, adjusted for increases in the cost of living. Of this amount, industry also urges that Congress designate at least $263 million for the human drug development and review process, which would include at least $110 million during Fiscal Year 1998 that industry is willing to pay in user fees under a reauthorized PDUFA.

Industry is concerned that the Administration's budget proposal for FDA in Fiscal Year 1998 would reduce budget authority by over $68 million – an 8 percent reduction in federal appropriations and a 13 percent cut in the budget for human-drug approvals. This reduction would occur entirely in the salaries and expenses account of FDA, which would be translated directly into reduced professional staff resources and slower delivery of new drugs to patients. Funding for FDA professional staff resources constitutes the major portion of the agency's budget. The work of qualified and dedicated staff is critical to FDA's efforts to streamline regulatory activities that promote and protect the health and safety of the American people.

The Administration's budget proposal appears to provide a 7 percent increase in FDA resources, but this is misleading because it includes $131 million in user fees for other industries that have been previously proposed and consistently rejected by Congress. It is irresponsible to suggest that FDA's budget for the next fiscal year will be increased when that increase is based on user fees that have never been authorized by Congress.

Funding FDA at the current level of $820 million as described above is essential under the bedrock principle that user fees must be additive to baseline appropriations, not a substitute for such appropriations. Otherwise, the user fees would simply be a means to promote general deficit reduction.

The Administration's budget proposal also would undermine the PDUFA program in another way. The Administration would reclassify user fees from "offsetting collections" to "governmental receipts." Such a reclassification would, in effect, be a new tax and would allow industry user fees to be expended for any Government purpose. That would contravene the user-fee principles that the fees be additive and dedicated to the drug-review process. For this reason, industry strongly opposes the reclassification of user fees as proposed by the Administration.

Without level funding for FDA, there inevitably would be a substantial slowdown in drug development and review times, to the ultimate detriment of patients. Industry believes that failure to provide level funding for FDA and thus renew PDUFA could jeopardize the nearly 50 percent reduction in FDA review times achieved under the 1992 user-fee law and produce delays of many months in moving new drugs from lab to market. With industry spending $19 billion on R&D this year to develop new cures and U.S. taxpayers providing $13 billion to NIH for biomedical research, it makes no sense to cut FDA's budget by $68 million and delay approval of these new cures.

FDA IMPROVEMENT LEGISLATION

To complement the user-fee provisions, industry's other FDA-improvement proposals are designed to structurally streamline the FDA so the agency's procedures are less cumbersome and are consistent with modern scientific and regulatory practices, not yesterday's standards.

Industry's current legislative proposals reflect many consensus views that emerged during the 104th Congress, and are based on what industry advocated in 1995-1996 and on legislation developed in the Senate and House in 1996. Specifically, the proposals are based on

S. 1477, sponsored by then-Senator Kassebaum, and H.R. 3199, introduced by Representative Richard Burr (R-NC). S. 1477 was approved by the Senate Labor and Human Resources Committee by a bipartisan vote of 12 to 4, with support from Senators Dodd, Harkin, and Mikulski. H.R. 3199 was co-sponsored by a bipartisan group of more than 200 House Members.

In seeking to build on this consensus, industry dropped provisions that did not receive widespread support, substantially modified others, and opened discussions with FDA on all aspects of drug development and approval. For example, industry dropped provisions that would have expedited FDA action on NDAs that had been approved abroad, required mandatory third-party reviews, and established a Policy and Performance Panel to oversee agency activities. Industry also modified provisions dealing with data on drug effectiveness to give the FDA flexibility to act, rather than to mandate action. Industry's proposals are reasonable; many are supported by FDA. They have been thoroughly discussed and analyzed, and they enjoy wide bipartisan support in Congress.

The provisions discussed below, as well as industry's other important FDA-improvement proposals, are set forth more comprehensively in Attachment B to this statement.

Data On Drug Effectiveness (See Attachment B, Sec. B. 2)

Problem: FDA accepts one well-controlled Phase III clinical trial with adequate supporting evidence to demonstrate effectiveness for biological products, but usually maintains that there is a legal requirement for two such Phase III trials for drug products. There is no justification in science or logic for this difference; it simply reflects the provisions of two different laws regulating two different kinds of medicines – the Biologics Control Act that applies to biologics and the Federal Food, Drug, and Cosmetic Act that governs drugs. As discussed below, the standard for drugs should be changed to require one well-controlled Phase III clinical trial with adequate supporting evidence to demonstrate effectiveness, to reflect changes in modern science and to be consistent with the requirement for biologics.

In Congressional testimony last year, Dr. Carl Peck, formerly Director of FDA's Center for Drug Evaluation and Research and currently Director of the Center for Drug Development Science at Georgetown University, stated, "The principle of requiring two, independent, empirical Phase III trials proving effectiveness, after much has already been learned about a drug's effectiveness in earlier phases of drug development, seems scientifically out of date."

In addition to saving substantial time and expense, Dr. Peck estimates that, rather than being required to participate in duplicative and redundant Phase III trials, "more than 25,000 human subjects annually could be redirected to other, more informative" clinical trials. Many sick patients would no longer have to take placebos in unnecessary trials, but instead could be given an appropriate therapy.

Reflecting the changing understanding of the power of modern scientific investigations and statistics, FDA has on occasion approved NDAs on the basis of one adequate and well-controlled Phase III trial and has even stated that it has the authority to do so. Yet, as detailed in a recently released draft *Guideline on Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* that outlines current agency practice, FDA still generally interprets the law to require two or more pivotal Phase III studies to provide substantial evidence of effectiveness, regardless of the scientific adequacy of the data. A related but separate problem involves the practice that has evolved under which sponsors routinely submit all studies and supporting documentation for NDAs and Supplemental NDAs (SNDAs) to FDA, regardless of whether they are relevant to the issue of efficacy and whether the data is excessive and thus unnecessarily burdensome to agency reviewers and applicants.

<u>Solution</u>: It is important to revise the law to give FDA the clear authority to decide on a case-by-case basis what scientific support is required to provide substantial evidence of effectiveness.

As discussed in FDA's draft *Guidance* mentioned above, approval in a particular case might be appropriate based on one adequate and well-controlled Phase III clinical trial. FDA should not be forced to overcome any presumption in any case regarding what kind and amount of evidence is necessary, so long as substantial evidence of effectiveness is provided.

Regarding the amount of effectiveness data currently required in applications, FDA acknowledges that sponsors submit too much data and recently indicated that it will consider summaries for efficacy studies that are not relied on to support label claims. A March 1997 draft *Guidance on FDA Approval of New Cancer Treatment Uses for Marketed Drug and Biological Products* proposes new efficacy-data requirements for FDA to encourage the filing of supplements, but this would merely codify existing practices and apply only to cancer drugs.

Industry proposes that the requirements for NDA and SNDA data submissions be streamlined, while preserving FDA's ability to be fully assured of a new drug's safety and effectiveness.

Improving the NDA/BLA Administrative Process (See Attachment B, Sec. D)

Problem: In the past, FDA did not pay sufficient attention to improving the efficiency of the NDA review process. Only recently has the agency begun to realize that administrative changes are essential to make the regulatory process more efficient and less time-consuming.

Solution: There are five areas where legislative changes are needed to ensure a sound administrative process: (1) requiring that important meetings be scheduled more promptly; (2) establishing the authority of agency officials who review NDAs over field personnel; (3) ensuring that important decisions are made at an appropriate level in FDA; (4) designating important FDA decisions as final agency action for purposes of judicial review, and (5) requiring the agency to establish adequate agency performance goals and objectives and to keep statistics so its performance can be evaluated.

Manufacturing Changes (See Attachment B, Sec. C. 3)

Problem: For drugs that have already been approved, only the most minor manufacturing supplement changes can now be made by a sponsor

without prior approval by FDA. The FDA's requirement for advance agency approval of most technical manufacturing changes results in a waste of scarce agency resources that could be better used in the drug development and review process. It also causes unnecessary delays in modernizing pharmaceutical production facilities and equipment. And it represents an economic handicap to U.S. manufacturers because new methods of manufacture can be implemented almost immediately in Western Europe and elsewhere in the world.

Solution: As recommended by the Clinton Administration in its "Reinventing Government" initiative, industry proposes to partially deregulate the process by which manufacturing changes are made. This would allow FDA to re-deploy scarce resources wasted in processing technical manufacturing supplements to the more critical drug development and review process.

FDA would determine the types of changes that must be pre-approved, those that could be communicated to the agency without requiring pre-approval, and those that would be so minor that they could be reported as part of a company's annual report. We believe FDA would agree with this basic structure, but legislative criteria must be provided to guide the agency.

The proposed changes would only modify the process by which manufacturing changes are regulated by FDA. Streamlined regulatory requirements would allow updated technologies to be introduced in a more timely manner. This procedural reform would not, however, materially change current quality and safety practices. All changes to an approved application would still be reported to FDA. All changes would still require full compliance with all Good Manufacturing Practices, including validation. All changes that affect the approved formulation or release specifications would still require advance approval. All manufacturers would still be required to conduct studies that support the approved specifications and quality attributes of their products.

In addition to the specific subjects discussed above, industry has other issues, including the dissemination of health care information, that merit the attention of this Subcommittee, the Committee on Commerce, and the full House of Representatives. BIO also offers for the Sub-committee's consideration a proposal to improve collaboration on breakthrough drugs that is described in Attachment C.

CONCLUSION

FDA must be fully funded for Fiscal Year 1998 so that it can carry out its many vital public-health responsibilities, including implementation of an improved and renewed user-fee law. A five-year, reauthorized user-fee program, together with related improvements, would provide FDA with enhanced resources and a streamlined structure and practices, enabling the agency to make more safe and effective new drugs available more quickly to more patients.

ATTACHMENT A

GENERAL PROVISIONS AND SPECIFIC PERFORMANCE GOALS IN PDUFA II

As suggested by FDA and industry, a reauthorized PDUFA would provide that user fees be adjusted each year to reflect inflation and changes in the agency's workload. The more FDA's drug and biologics workload increases, the more the agency would receive in user-fee payments. The framework also would enable FDA to install a paperless, electronic information system to process all required submissions and applications.

Unlike the 1992 law, the 1997 version would allow user fees to support third-party reviews authorized by FDA. To implement floor statements made by Members of Congress at the time the 1992 law was enacted, the legislative framework developed by FDA and industry would exempt all designated orphan products from application fees, as long as there are no non-orphan indications in the applications. The framework also would simplify and liberalize the current small-business exception, and exempt from application fees those applications and supplements submitted to support pediatric indications for products primarily intended for adults. FDA has urged sponsors to initiate new or supplemental applications to support pediatric uses and doses for drugs already approved for adults.

Clinical-Development Provisions

Following are the performance goals that would be established for the clinical-development phase (from the filing of an Investigational New Drug [IND] application to begin testing in humans to the filing of an NDA) of the drug-regulatory process:

- **Timelines would be established for setting key meetings, ranging from 30 to 75 days depending on the nature and urgency of the subject. For example, meetings prior to IND or NDA filings would occur within 60 days of the FDA's receipt of a request for a meeting.**

- **FDA would be required to respond to a sponsor within 30 days of a sponsor's answer to the issuance of a clinical hold on beginning human trials.**

- **FDA would be required to provide written protocol agreements within 45 days, and adhere to them, so criteria for accepting**

the design or results of a clinical study could not be changed, unless public-health concerns unrecognized at the time of protocol assessment become evident.

- **A two-tier appeals process would be established to resolve scientific disputes between sponsors and FDA, with timelines for action.**

Drug-Review Provisions

Following are the performance goals that would be established under the proposed legislative framework for the drug-review process:

- **"Approvable" letters would be replaced by "complete response" letters that would clarify and help expedite the way in which reviews would be completed.**

- **FDA would be required to clearly distinguish between NMEs and other products submitted for review to ensure that the agency focuses on the most important products – NMEs.**

- **Review time for standard therapies would be reduced from 12 to 10 months and for manufacturing supplements from six to four months.**

- **FDA would explore ways to reduce review time for priority new drugs below the six-month deadline in the 1992 law.**

- **Review time for resubmissions would be reduced, commensurate with the complexity of the data submitted.**

- **A defined process would be established for FDA to request information from NDA applicants during the review period.**

For each of the five years of a reauthorized user-fee law, FDA would provide timelines for implementing each of the performance goals specified above – which would require a five-year reauthorization to ensure adequate planning, allocation of resources, and monitoring of results. For example, for reviewing standard NDAs, FDA would commit to reviewing 90 percent in 12 months during Fiscal Year 1998. During Fiscal Year 1999, FDA would review 30 percent of standard NDAs in 10 months and each year thereafter would review a higher percentage of standard NDAs in 10 months, up to 90 percent during Fiscal Year 2002.

ATTACHMENT B

FDA IMPROVEMENT PROPOSALS

A. Improving the IND System

The current Investigational New Drug (IND) provisions in Section 505(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) are extremely short and contain few requirements. Most of the current IND system has been created administratively by FDA.

As a result of recent administrative reforms, many of the problems with the IND system have been reduced or are, in any event, not sufficiently serious to justify a high legislative priority. The three areas where legislative change is needed involve (1) IND data requirements, (2) FDA use of clinical holds, and (3) duplication of IND review by both FDA and NIH.

1. IND Data Requirements

For many years, FDA required exhaustive background information on a drug to be submitted in an IND even for a Phase I clinical study. Faced with the realization that clinical trials increasingly were being conducted abroad because of the more efficient system developed there, and under programs to eliminate unnecessary paperwork, FDA has begun to relax this requirement.

This problem deserves to be resolved by legislative directive, through amendment of the current statutory authority relating to clinical investigation of new drugs in Section 505(i) of the FD&C Act. An IND should be required only to contain adequate reports of basic information necessary to assess safety. In particular, detailed information should not be required for Phase I and II clinical trials.

2. Clinical Holds

Under current FDA policy (not required by the FD&C Act itself), a sponsor submits an IND to FDA and must not begin the clinical study for a period of 30 days during which FDA reviews the IND. Unless FDA issues a formal written clinical hold prior to the end of the 30 days, the sponsor may then begin the clinical study.

During the past decade, FDA has issued clinical holds for up to 15 percent of INDs submitted to the agency. In some instances, clinical

holds have been based solely upon safety concerns, but, in other instances, FDA personnel have based clinical holds on their views regarding protocol design and drug effectiveness as well. As a result of recent administrative reform, these problems have been reduced, but the use of clinical holds remains highly variable and subjective among FDA personnel.

When a sponsor responds to a formal clinical hold, there is currently no FDA policy or practice that requires the agency to act upon that response within any time whatever. In practice, months can go by without an FDA decision, during which the clinical trial remains on hold. The agency has recently informally agreed to take action under these circumstances within 30 calendar days for 75 percent of these submissions this year and increasing to 90 percent in subsequent years.

To shorten review times and reduce the considerable expense of clinical investigations, clinical holds should be based solely on safety concerns, and any response to a hold should be required to be provided by the agency within 30 days after receipt of a submission from the sponsor.

3. <u>Duplicative NIH review of INDs</u>

In the mid-1970s, as a result of the remarkable developments in the field of biotechnology, the National Institutes of Health (NIH) established a recombinant DNA advisory committee (RAC) to review all protocols for the investigation of recombinant DNA products. At that time, there was no clinical research involved. As clinical research into human gene therapy began, however, duplicative reviews of protocols were undertaken by FDA and NIH. FDA required the submission of an IND, which the agency reviewed in detail. NIH continued to require the submission of basically the same information, which the RAC also reviewed in detail. Indeed, under FDA regulations, an independent institutional review board (IRB) was also required to review the protocol before submission of the IND to the agency, to assure the protection of human subjects. Thus, NIH review of protocols that have already received review and approval by an IRB and FDA has become redundant.

It has been suggested that the RAC provides a useful function in reviewing the ethical as well as the scientific aspects of biotechnology protocols. In fact, however, the IRB and FDA do exactly the same thing. There is no aspect of a clinical investigation involving biotechnology products that the RAC can do in addition to, or better than, an IRB and FDA.

Eliminating the duplicative RAC review will shorten the time and reduce the expense required for investigation of new biotechnology products. There will be no loss of public health protection.

B. Improving the NDA/BLA Review and Approval Process

For many years, FDA insisted that its process for reviewing and approving New Drug Applications (NDAs) and Biologics License Applications (BLAs) was adequate and did not need improvement. Numerous prestigious study commissions nonetheless recommended significant changes in this process, the latest of which was the White House "Reinventing Government" Performance Evaluation Review. FDA has been incorporating some, but not enough, reforms in guidance documents. It is, therefore, essential to incorporate into statutory language both the reforms that FDA itself has been adopting and reforms that the agency has not yet addressed, in order to assure that improvements in the NDA/BLA review and approval process are not weakened.

These reforms include the following six areas: (1) improving the license process for biologics, (2) clarifying the data needed for showing drug effectiveness in an NDA/BLA, (3) authorizing approval of an NDA/BLA on the basis of pilot or small scale manufacture, (4) eliminating unnecessary environmental analysis for an NDA/BLA, (5) assuring the independence of advisory committees, and (6) removing the prohibition against statements that an NDA has been approved for a new drug. Each of these is discussed in greater detail below.

1. Improve the Process for Biological Products

The law governing the review and approval of licensing applications for biological products was originally enacted in 1902 and has not since been substantively amended. Under the 1902 Act, separate establishment and licensing applications have been required. Recognizing the need to make this process more efficient, FDA has recently moved to consolidate these two separate review and approval processes into one Biologics License Application (BLA). The Public Health Service Act should be amended to codify these changes.

Because biological products and new drugs have long been subject to separate and distinct statutes -- the Biologics Act of 1902 and the Federal Food, Drug, and Cosmetic Act of 1938 -- and their administration and implementation have been the responsibility of two separate and distinct governmental organizations (currently the Center for Biologics Evaluation and Research (CBER) for biological products and the Center for Drug Evaluation and Research (CDER) for new drugs), the procedures and requirements for these products have diverged

substantially. Differing requirements have been applied to a new drug/biological product depending upon which FDA component has been assigned responsibility for it, rather than upon the nature of the product under review. Although some effort has been made to conform the procedures and requirements applicable to biological products to those for new drugs, this effort has been slow and uncertain.

2. Data on Drug Effectiveness

For many years, FDA has enunciated inconsistent and confusing positions on the number of clinical studies needed to demonstrate the effectiveness of a new drug. On the one hand, FDA has stated that the law requires a minimum of two adequate and well controlled Phase III clinical trials for NDA approval. On the other hand, FDA has in fact approved a number of NDAs for important new drugs on the basis of one adequate and well controlled Phase III trial and has stated that it has the authority to do so. The Center for Biologics Evaluation and Research has, in fact, stated that one trial is ordinarily enough and that two trials represent an exception. There are important implications for patients. Those enrolled in unnecessary efficacy trials may be part of control groups receiving placebos, when they could be benefiting from needed therapies. The review of these unnecessary data also unduly burdens FDA and delays approval of important new medicines.

Very recently, FDA has issued a guideline that candidly states that the agency will in fact approve an NDA on the basis of one adequate and well-controlled Phase III clinical trial where the totality of the scientific evidence is sufficient to demonstrate effectiveness. FDA officials have also pointed out that, on rare occasions, FDA may waive completely the requirement of even one adequate and well-controlled Phase III trial where such a trial would be unethical and unnecessary to determine effectiveness. It is important to revise the requirements of the FD&C Act to reflect these FDA policies and assure that FDA practice is consistent with both the letter of the law and the expectations of Congress.

As a separate matter, under current FDA regulations, an NDA is required to contain all studies, of any kind, ever undertaken with respect to the new drug. Each of these studies is required to be reported. Insufficient distinction is made between those early studies designed to obtain preliminary information on the drug and the later pivotal study or studies designed to obtain the data on safety and effectiveness on the basis of which FDA approval will be requested. As a result, not only are

the NDAs lengthy and complex, but FDA reviewers may spend as much time on unimportant studies as they do on the pivotal studies.

There is general agreement that excessive and unnecessary information regarding effectiveness data from early trials is being submitted in NDAs in the form of detailed reports for studies where the level of detail is not required to make a regulatory decision. Eliminating this level of detail would reduce preparation time on the part of industry and review time on the part of FDA. FDA and industry have agreed that early studies that are not regarded as pivotal should be included in the NDA in the form of abbreviated submissions. An abbreviated submission contains much less detail of study design and results and does not contain case report tabulations regarding the effectiveness of the drug. Only pivotal studies would be submitted in the detailed form that is currently used for all studies on effectiveness. Thus, the studies would still be available to reflect safety data and any other information that might be useful, but in much shorter and more concise form.

With respect to the pivotal studies on drug effectiveness, there remains some disagreement between FDA and industry with respect to the level of detail needed in the reports submitted as part of the NDA. Industry feels that FDA reviewers ask for excessive detail and do excessive re-analyses. FDA responds that its independent scientific evaluation of the pivotal studies is an extremely important part of the NDA review process. Both FDA and industry do agree, however, that once the extent of detail to be submitted for a pivotal trial has been agreed upon, individual FDA reviewers should not be permitted to request additional information without obtaining the approval of their supervisors.

3. Pilot and Small Scale Manufacture

FDA has often required in the past that, before an NDA or BLA can be submitted, the applicant must scale up from a pilot or small scale plant to a full commercial facility in order to conduct stability studies on the final product and to submit a full description of the manufacturing process as part of the submission. This has substantially delayed the submission of applications for new drugs and biologics and has increased the cost of these submissions. It has required a substantial investment in manufacturing facilities before the applicant can be certain that the drug will in fact be approved. In some notorious instances, manufacturing plants have been built, but the drug has not been approved. FDA has now agreed that product approval can properly be based on pilot or small scale manufacture. This policy should be incorporated directly in the statute.

4. Environmental Analysis

The National Environmental Policy Act (NEPA) of 1969 requires all federal agencies to consider the environmental impact of any major action they take that may significantly affect the quality of the environment. Under this statute, FDA has required environmental impact analyses to accompany every NDA, even though such analyses rarely, if ever, have any bearing on NDA approval. Industry estimates that it costs at least $200,000 to conduct this analysis for each NDA. In turn, FDA must also expend resources reviewing the analyses. There is general agreement that these rarely serve any useful purpose in the IND/NDA review process and should be eliminated, except where a Center director demonstrates that a drug is likely to have a substantial environmental impact.

5. Advisory Committees

Although advisory committees had been used by FDA on an ad hoc basis throughout this century, the current approach of using scientific technical advisory committees to assist in the evaluation of important new drugs began in the early 1970s, under regulations promulgated by FDA at that time. Although the use of advisory committees is generally regarded as an important element of the IND/NDA review process, there has been substantial criticism about specific deficiencies in the way that the advisory committee process currently works.

Many advisory committees are selected and administered by the very FDA divisions whose work they are intended to evaluate. Advisory committees often do not meet frequently enough to assure timely review of important matters. The affected industry often is not always given the same information that is provided to the advisory committee, is not permitted to respond at open advisory committee meetings when inadequate or incorrect information is provided by others, and is relegated to an insignificant position in the process. After advisory committee decisions are made, it may take months or years before any FDA action is taken.

All of these deficiencies can readily be corrected, drawing upon the example and practice of other federal agencies, to restore the integrity and credibility of the advisory committee process. Advisory committees should be selected and administered in the Office of the Commissioner, not at the reviewing level. Steps should be taken to assure their independence. The representatives of companies whose drugs are being reviewed should routinely be given all of the relevant materials that

are sent to the advisory committee and should be provided an opportunity to participate fully in the advisory committee process at any time, to the same extent as FDA representatives. Once the advisory committee has made a recommendation, FDA should be required to act on it promptly.

6. Marketing Approval

Section 301(l) of the FD&C Act provides that it is illegal to state in the labeling or advertising for any new drug that FDA has approved an NDA for the drug or that the drug complies with the requirements of Section 505 (which requires FDA approval of an NDA prior to marketing). This provision was originally enacted when FDA merely allowed NDAs to become effective, and did not explicitly approve an NDA. It is essential today that industry explicitly inform physicians, healthcare institutions, the investing public, and others when FDA has approved an NDA for a new drug. Section 301(l) should be repealed.

C. Improving the NDA/BLA Post-Approval Process

Following FDA approval of an NDA or BLA, numerous important post-approval regulatory requirements are imposed. These post-approval requirements have a major impact on the dissemination of information about the drug and the methods by which the drug can be manufactured.

During the past several years, there has been substantial criticism that, because of these FDA post-approval requirements, important scientific information is withheld from practicing physicians and health care institutions and that manufacturing procedures in the United States lag behind those available abroad. FDA has begun to address these issues, but the progress has been slow. It is apparent that legislative action is necessary to ratify promising reforms and assure that they are accepted in practice throughout the agency.

The specific issues on which new legislation is needed relate to (1) dissemination of scientific and medical information to physicians and health care institutions, (2) the dissemination of health economics or pharmacoeconomic information, (3) the degree of FDA regulatory control needed for manufacturing changes, (4) the type of medical information needed to permit the addition of new uses to the labeling for already-approved new drugs, and (5) regulatory control over pharmacies that manufacture new drugs.

1. Dissemination of Scientific Information

FDA imposes very strict control over the dissemination of any medical or scientific information, of any type, relating to an approved new drug. FDA takes the position that only claims that are approved by FDA as part of the NDA for the drug may lawfully be made.

Once a new drug is approved for marketing, however, new medical and scientific information invariably comes to light within a very short period of time. Interested clinicians experiment with the use of the drug, publish the results of their studies, send letters to medical journals relating significant case histories, give talks on their clinical experience at medical meetings, and thus widely disseminate new information about the use of the drug in daily medical practice. As a result, there quickly develops a body of medical literature that is outside the package insert approved by FDA.

Much of this new information is important to the health and lives of individual patients. A physician who is familiar with the latest information is in a far better position, for example, to save the life of an extremely ill patient than a physician who relies solely upon the FDA-approved package insert. Yet FDA forbids any drug manufacturer to disseminate the very type of information that could be of greatest importance in promoting health and quality of life unless an unsolicited request is received.

FDA has attempted to respond to this by encouraging the industry and the medical profession to submit information that would permit adding new uses to the package insert for an approved drug more expeditiously. Thus far, this approach has not succeeded. It is clear that a different approach is needed to liberalize the sharing of information from such sources as peer-reviewed literature without the current regulatory limitations.

2. Pharmacoeconomic Information

In the new era of managed care, drug companies must deal directly with health care institutions to provide timely information on the most effective and efficient use of drugs to improve patient health and reduce health care costs. At present, however, FDA takes the same regulatory approach toward health care economic information as it does toward claims about drug safety and effectiveness, despite the fact that economic claims may be related to the approved labeled uses of a drug.

As a result, the pharmaceutical industry is prevented from providing to health care institutions the very information they need to improve quality of care while also saving costs. FDA has stated that pharmacoeconomic claims must be supported by adequate and well-controlled clinical trials and may not be based on economic projections and analyses of the type that businesses have used in every other segment of the economy for decades.

Legislation was introduced in the House last year to address both dissemination of information and pharmacoeconomic claims. Senators Mack and Frist also introduced legislation in the Senate in 1996 to address these matters, and they are again collaborating to develop a more refined version of that legislation, based upon comments received in the past year. Before considering other approaches, it might be advisable to await further legislative developments.

3. Manufacturing Changes

Improvements in the method of manufacture almost always occur after approval of an NDA. Nonetheless, they cannot be put into practice because they would violate the conditions of NDA approval. Instead, a supplemental NDA must be submitted to justify the new method of manufacture, which entails unduly lengthy review periods. While applicants await review, of course, additional manufacturing changes have been found. They, too, cannot be used. Thus, it is a vicious cycle. The method of manufacturing used in the United States can be years behind the actual manufacturing techniques that could be used if it were not for the requirement of unnecessary FDA pre-approval.

There are two ways to approach this problem. First, FDA could speed up the approval of new methods of manufacturing new drugs. FDA has, in fact, made considerable progress in this direction. Even with this improvement, however, the use of modern drug manufacturing methods in the United States is unnecessarily restricted. Second, many of the manufacturing changes that now require FDA approval could be simply deregulated, as was suggested by the Administration's commendable Reinventing Government report on drugs. Despite the President's leadership, however, and after years of effort to reach agreement on criteria for exempting new methods of manufacture from the requirement of FDA approval, relatively little progress has been made.

Further progress in permitting rapid implementation of new manufacturing technology will require legislative action. Three types of manufacturing changes should be described: those that do not require FDA review and approval, those that do require FDA review and approval, and those for which FDA should have notification prior to implementation, but only a limited period within which to conclude that approval is required. New legislation should establish or characterize the criteria for these three categories, but leave the details of deregulation to FDA on the basis of experience in interpreting and applying these criteria through regulations and guidelines over the coming years.

4. Supplemental NDAs for Labeling Changes

As noted above, current drug labeling inevitably lags behind current medical practice, in some instances by many years. Part of the reason for this problem is that FDA insists on the same quantity and quality of scientific evidence to support a labeling change to incorporate a new use for an approved drug as it does to support the initial labeling for

the product. In short, FDA disregards the scientific literature and reliable reports of clinical practice and instead requires controlled studies to support a new use for an approved drug.

Under the current FDA approach, ethical problems arise when patients are being given placebos and it is common knowledge and experience that the new use represents not only sound medical practice, but often the preferred treatment.

Following the failure of its attempts to obtain controlled trials to support widespread new uses for approved drugs from either the medical profession or the regulated industry, FDA has begun to realize that it must instead reconsider the criteria it has traditionally required for approval of these new uses. A recent draft guideline states that FDA may consider literature references, case reports, and other forms of clinical evidence short of controlled trials to support a new use for an approved drug. Although FDA emphasizes the use of this approach in the area of oncology, there is no basis for restricting it to any particular pharmacologic class of drugs. The same criteria should apply to the evaluation of new uses for approved drugs of all kinds.

Legislation is needed to assure that the new FDA policy will have adequate statutory support and will endure in regulatory practice. The law should therefore be amended to permit the use of whatever scientific and clinical evidence is sufficient to assure that an approved drug is effective for a new use, based on the totality of all the information available. Such a standard is less than that used for the initial approval of a new drug, but nonetheless sufficient to assure that labeling will remain consistent with current good clinical medicine practices and thus be responsive to the needs of both physicians and their patients.

5. <u>Pharmacy Manufacturing</u>

In recent years, some large pharmacies have begun to manufacture drugs in an essentially unregulated environment, unlike the environment in which the pharmaceutical industry operates. These pharmacies do not compound an individual drug on the order of a licensed physician for an identified individual patient, but rather manufacture large quantities of drugs and advertise their availability to the medical profession at large. As a result, a substantial amount of drugs has been marketed without any form of FDA regulation or approval.

Without question, pharmacies should enjoy the professional privilege of compounding a particular drug on the order of a licensed physician for an identified individual patient. At the other extreme, however, pharmacies should not be permitted to go into the business of manufacturing drugs without obtaining the same FDA approval as any other drug manufacturer. New legislation is required to draw a clear line between the practice of pharmacy and the manufacture of drugs.

Where a pharmacist repeatedly receives orders from physicians for identified individual patients, there is no need for the pharmacist only to prepare enough of the drug for a single order. Under these circumstances, limited quantities can legitimately be prepared for expected future orders as well. It must be made clear, however, that the pharmacist may only advertise the availability of a compounding service in general, and may not advertise or otherwise promote the compounding of a particular drug or any category of drugs. In short, the legislation must make clear that the practice of pharmacy retains its traditional scope and does not include the business of manufacturing significant quantities of drugs for broad distribution.

D. Improving the NDA/BLA Administrative Process

Administration of the FDA process under which new drugs are regulated requires a major effort. Efficient administration can expedite the process, and inefficient administration can slow it down, wholly independent of the scientific aspects relating to the testing of a drug for safety and effectiveness. In the past, FDA has virtually ignored many of the most pressing management issues relating to the efficient administration of the NDA review process. Only recently has the agency begun to realize that administrative changes are essential to an efficient regulatory process. The five areas where legislative changes are needed to assure a sound administrative process are (1) requiring that important meetings be scheduled more promptly, (2) establishing the authority of agency officials who review NDAs over field personnel, (3) ensuring that important decisions are made at an appropriate level in FDA, (4) designa- ting important FDA decisions as final agency action for purposes of judicial review, and (5) requiring the agency to establish adequate agency performance goals and objectives and to keep statistics so its performance can be evaluated.

1. Meetings

For years, one of the most frustrating aspects of the IND/NDA system was that it was very difficult to obtain timely meetings with FDA to discuss important regulatory issues. Companies were forced to delay clinical testing for months until a meeting could be obtained to discuss a proposed clinical trial protocol. Even the most simple questions often went unanswered. Sponsors and applicants were forced to make decisions without adequate FDA advice, often leading to misunderstanding and wasted time and effort.

Substantial progress has been made in this area under the Prescription Drug User Fee Act of 1992. As part of the discussion relating to reauthorization of user fees, a formula has been developed under which meetings would be scheduled within 14 days of a receipt of a request and the meeting itself would be held within 30-75 days of the receipt of the request depending upon the type of meeting. The formula would begin by achieving 70 percent compliance immediately and working up to 90 percent compliance in fiscal year 2001. There should be no excuse for failing to schedule and actually to have a timely meeting on a significant regulatory issue. Accordingly, new legislation is needed to assure that proper FDA attention is given to this matter.

2. FDA Field Personnel

It is not unusual, after FDA headquarters personnel have spent months reviewing and approving an NDA, for the FDA field personnel to determine that the manufacturing and controls approved for the new drug are nonetheless inadequate. At times, in fact, inaction by field personnel assigned to conduct a premarket approval inspection of the manufacturing facility for a new drug has resulted in a delay in the approval of an NDA. Although the FDA field personnel are essential to the regulatory work of FDA, it must be recognized that the reviewing medical officers and other personnel at the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research take precedence in the determination of the safety, effectiveness, proper labeling, and adequate manufacturing controls and procedures for every new drug.

Legislation is needed to assure that the field personnel have an adequate opportunity to make their views known to the headquarters personnel reviewing and approving an NDA, but that the final authority on all matters involving an NDA rests in the reviewing personnel, not the field personnel. If the reviewing office concludes that its written decisions should be changed on any matter, based on a field report, that should of course be done. Under no circumstances, however, should the field be able to overrule the headquarters personnel. Nor should delay in the field require that final action on an NDA be deferred, unless there is a substantial public health issue that has been identified which justifies such a delay.

3. Delegation of Authority

Under the current wording of the FD&C Act, all administrative authority is given to the Secretary of Health and Human Services (HHS). The Secretary has delegated this authority to the Commissioner of Food and Drugs. In many instances, this authority has been redelegated to relatively low levels within FDA.

For some FDA functions, a relatively high official within the agency should make the final decision. Some of the legislative amendments to the statute establish the specific level at which these decisions are to be made. Rather than include in each one of these provisions an explicit nondelegability clause, it is simpler to include a

single provision that provides for nondelegability under each of these provisions as a general administrative housekeeping measure.

4. Final Agency Action

At present, there is only one way that a sponsor or applicant can challenge an adverse agency determination relating to an IND or an NDA. The statute provides that court review can occur only after an NDA is denied, an administrative hearing is held, and the Commissioner has made a final determination based upon the administrative record from the hearing. As a practical matter, that means that judicial review is never feasible on important final agency decisions that occur during the IND/NDA process.

Judicial review should not be available with respect to every minor event in the IND/NDA process, but it should be available for the most important events. It should, for example, be an option when FDA establishes a clinical hold or denies a request to remove a clinical hold, or when an NDA is disapproved or revoked. It should also be available on any other important regulatory decision where FDA has itself reviewed the matter extensively as part of its internal appeal process and has come to a final decision. Finally, it should be available where the agency has determined that a matter is sufficiently important to send a warning under Section 309 of the statute. In each of these situations, there is a clear and final agency decision relating to the matter and thus there is no basis for determining that the issue has not received adequate FDA attention or does not represent the final and authoritative position of the agency on that particular matter.

5. Policy and Performance Review

Concern has frequently been expressed that FDA does not have a clear mission statement, does not have formal written strategic and performance plans, does not attempt to set objective, quantifiable, and measurable performance goals, does not keep statistics adequate to measure its performance, and does not issue a yearly report that compares actual results with established goals and objectives. Congress enacted the Government Performance and Results Act of 1993, 107 Stat. 285, to require precisely this type of agency planning throughout the government. Thus, all that is needed is to assure that FDA develops precisely the type of strategic and performance plans and reports that are now required by the 1993 Act for the entire federal government, beginning no later than September 30, 1997.

E. Pediatric Research

Prior to FDA approval of an NDA for a New Chemical Entity, the drug must be studied in humans to demonstrate that it is safe and effective. These initial clinical studies are almost always conducted in adults. The vast majority of drugs thus remain labeled solely for adults, for both ethical and practical reasons.

Physicians prescribe drugs for children based upon differences in body weight and general clinical experience. There are many reasons that new drugs are not studied in children either before or after approval of an NDA. Drug formulations for children often pose significant technical obstacles. Manufacturers and clinical investigators are concerned about liability issues. Obtaining informed consent for a minor, and especially an infant, is a major obstacle. Many parents are reluctant to give consent. Compliance with the test regimen can present significant problems. Unless incentives are incorporated into the law to help counter these disincentives, it remains unlikely that any significant testing of new drugs in children will occur either before or after NDA approval.

Legislation to provide a specific term of market protection against generic competition, in return for testing in children, would under some circumstances provide a clear economic incentive for such testing. It must be recognized, however, that this incentive would work only in those situations where generic competition does not already exist. Where generic competition exists, there is no incentive of any kind for the pioneer or the generic company to conduct testing in children.

In order to provide an incentive for testing on children, therefore, it is essential to provide a period of market exclusivity that extends beyond either the end of the current period of market exclusivity or the end of the patent protection, whichever is longer. Unless this is recognized, there will be no positive incentives to undertake difficult tests on children for those drugs where the patent term exceeds the period of market exclusivity.

There is substantial debate about the appropriate additional term of market exclusivity that would be sufficient to induce pharmaceutical companies to conduct testing on children. The research-intensive pharmaceutical industry is convinced that, at the very minimum, this would be one year. There may well be a number of drugs, however, where an additional one year of market exclusivity would not be sufficient to justify

the challenge of conducting tests in children. The choice between a shorter (one year) and a longer (such as a three year) period of market exclusivity should be left to the determination of the Secretary of HHS, in each case, based on the complexity and time required for completion of the study. It is possible to enact legislation that will provide an economic incentive for testing in children under all circumstances, except where a generic competitor is already on the market. The period of market exclusivity to be provided in the legislation is a policy decision for the Congress. A shorter (one year) period will provide a modest incentive, whereas a longer (three year) period will provide a more robust incentive.

F. National Uniformity

The FDA currently regulates food, drugs (including biological products), cosmetics, and medical devices in a comprehensive and coordinated way. FDA establishes regulatory policy under the FD&C Act, the Biologics Act of 1902, the Poison Prevention Packaging Act, and the Fair Packaging and Labeling Act, and that policy is implemented throughout the country. Because there is a national distribution system for all FDA-regulated products in the United States, it is essential that a complementary national regulatory policy be retained as well.

For the past century, federal and state food and drug law officials have sought to achieve consistency among the federal and state laws governing FDA-regulated products. For the most part, this has been achieved. In many important respects, however, this effort has failed, with the result that individual states have enacted local requirements in addition to those established by Congress and FDA. When this has happened, it has severely disrupted the national marketing system for FDA-regulated products.

Ten years ago, for example, the voters of California enacted an Initiative Measure requiring public warnings about FDA-regulated products for which FDA has determined that no such warnings are justified. Recently, California has taken action to force the use of warnings for calcium products because of a naturally-occurring lead content that FDA had already determined to be safe. FDA has itself urged California not to require warnings where FDA has determined that they are not appropriate, but to no avail. Similar legislation has been defeated in other states, but is now making a resurgence.

Calcium is, of course, an essential nutrient. Calcium deficiency results in osteoporosis, one of the most serious diseases for elderly women. Unjustified public warnings about the lead content of calcium will only exacerbate an already serious public health problem.

This is but one example of what occurs when state laws are enacted that add requirements to those determined by Congress and FDA to be appropriate for FDA-regulated products. To prevent further conflict and consumer confusion, Congress should enact a requirement for national uniformity in the regulation of food, drugs, cosmetics, and medical devices.

It is not enough simply to require national uniformity in the labeling of these products. The California law, for example, applies to all forms of public notification. Thus, national uniformity must be required for any form of public notification.

A national uniformity provision should explicitly recognize the right of state and local officials to enforce their own laws that are not in addition to or inconsistent with federal law. Thus, state officials should not in any way be hindered in enforcing laws and regulations identical to federal laws and regulations. It is only where the state law and regulations are different that state enforcement should be precluded.

In addition, traditional state prerogatives relating to drug reimbursement and the practice of pharmacy, including drug substitution standards, would not be affected. The FD&C Act includes a number of other provisions exempting the practice of pharmacy from coverage.

There may be appropriate circumstances where a state can show compelling and unique local conditions that justify an exception from national uniformity. Under these circumstances, FDA should be authorized to grant an exemption from the general rule of national uniformity.

Similarly, there may be circumstances where state action is essential to address an imminent hazard to health that is likely to result in serious adverse health consequences or death. Here, too, state action should be permitted while a petition for exemption is under consideration by FDA.

Finally, national uniformity should apply only to federal regulatory requirements and prohibitions, not to tort liability. The product liability law of any state should not be modified or otherwise affected by national uniformity in regulatory requirements.

ATTACHMENT C

BIO PROPOSAL TO IMPROVE COLLABORATION ON BREAKTHROUGH DRUGS

FDA has several programs designed to facilitate early access to new therapeutics for serious or life-threatening diseases. These were created at different times without attempting to integrate or harmonize them. One, the accelerated approval program, has successfully been used to speed the approval of new drugs for the treatment of AIDS. The program has not been more generally applied to other serious and life-threatening diseases. This is in part because the definitions and pathway for seeking accelerated approval lack clarity. Another, the priority products program, designates important new drugs to receive a six month review cycle, rather than the standard twelve month review cycle. But since priority products don't receive "priority" designation until a marketing application is submitted, there is no priority given until after the drug development process has been completed. With the development of an Accelerated Study and Approval Program (ASAP), FDA and sponsors can improve on the present program and reduce the development times for important new therapies.

Key to this new approach is not only a firm definition of "serious and life-threatening" for determining eligibility but also the establishment of a formal program to encourage early interaction between the Agency and sponsors who anticipate seeking accelerated or priority approval for their products. A "priority" designation should be promptly made following application by the sponsor. Where appropriate, FDA and the sponsor would collaborate to identify those surrogate endpoints that can serve as the basis for approval. Designated priority products would be eligible for faster meeting times, closer collaboration during development, submission of rolling applications, and a six month review under PDUFA.

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AMGEN

ON BEHALF OF

THE BIOTECHNOLOGY INDUSTRY ORGANIZATION

AND

THE PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA

BEFORE THE

SUBCOMMITTEE ON HEALTH AND ENVIRONMENT

COMMITTEE ON COMMERCE

UNITED STATES HOUSE OF REPRESENTATIVES

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